Evidence for a Hydroxide Ion Catalyzed Pathway in Ester Hydrolysis in Supercritical Water**

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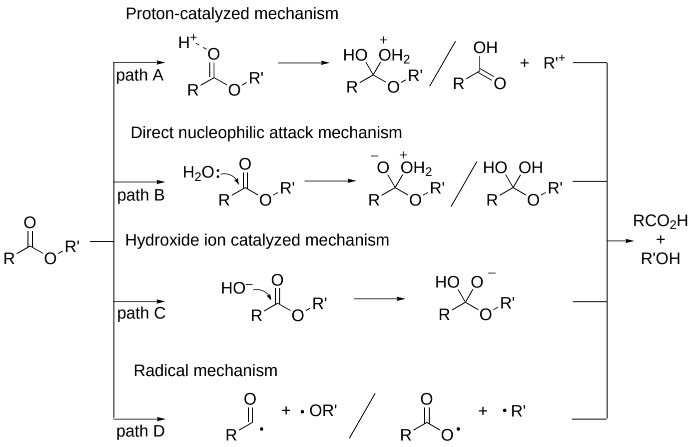
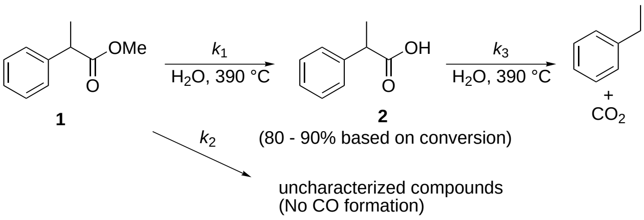
Supercritical water (SCW) has attracted much attention as a novel reaction medium from scientific and technological viewpoints.[1] It is the most environmentally benign solvent[2] and possesses high dissolving power for a variety of nonpolar organic compounds because of its weaker hydrogen-bond network[3] and lower dielectric constant[4] relative to ambient water. Furthermore, the discovery of the catalytic activity of SCW makes it a promising unique reaction medium for synthetic organic chemistry.[5, 6]

Among various organic reactions in SCW, hydrolyses of esters and amides are of interest for the decomposition and the recycling of poorly biodegradable synthetic polymers such as poly(ethylene terephthalate).[7] However, in spite of quite a few reports on practical applications, understanding of the detailed mechanism of this hydrolysis is still quite limited. Although an "autocatalytic" mechanism, in which the carboxylic acid produced by hydrolysis catalyzes the reaction (Scheme 1, path A), was proposed by analogy with the mechanism of nitrile hydrolysis,[1b, 8] no detailed mechanistic studies have been performed until recently. A mechanistic study in sub- and supercritical water revealed that the rate of hydrolysis decreases significantly near the critical point,[9] and the results were explained by a change in mechanism from acid-catalyzed reaction in subcritical water to direct nucleophilic attack of water in SCW (path B). Since the dissociation constants of carboxylic acids decrease considerably in SCW,[10] a negligible effect of the acid generated by hydrolysis seems reasonable, although the validity of the proposed mechanism has remained unclear.[11] We were intrigued by the possible involvement of hydroxide ions dissociated from SCW (path C), because base-catalyzed hydrolysis proceeds much faster than the acid-catalyzed reaction under ambient conditions. A radical-mediated reaction, for example, homolytic cleavage of the C–O bond of esters (path D), may also be possible, because the reaction in SCW is conducted at high temperature.



Scheme 1. Possible mechanisms of ester hydrolysis in SCW.

To clarify the mechanism, we performed kinetic studies on the hydrolysis of methyl 2-phenylpropionate (**1**) in SCW at 390 °C and various water densities. This compound was selected so that hydrolysis via the radical pathway involving direct C–O cleavage could be detected by means of the radical-clock decarbonylation reaction of the acyl radical intermediate.[12] We also examined the effect of protons and hydroxide ions to clarify their catalytic role. In sharp contrast to the previous mechanistic proposal, we found that hydroxide ions indeed catalyze ester hydrolysis in SCW. Among organic reactions in SCW, those catalyzed by hydroxide ions are less common than those catalyzed by protons. Therefore, our results shed new light on the mechanisms of organic reactions in SCW.



(1)

We first examined the hydrolysis of **1** in SCW [Eq. (1)] in a cylinder-type reactor at 390 °C and a water density of 0.34 $g\,cm^{-3}$ for 4 min, and the reaction mixture was analyzed by GLC (gas–liquid chromatography), GC-MS (gas chromatography–mass spectrometry), and NMR spectroscopy.[13] The ester mainly yielded carboxylic acid **2**, methanol, and a small amount of ethylbenzene. Analysis of gaseous products revealed the formation of carbon dioxide, but carbon monoxide could not be detected at all. The absence of carbon monoxide indicates that the direct homolysis of the C–O bond is unlikely. We also found that carboxylic acid **2** transformed into ethylbenzene under the above reaction conditions with the loss of carbon dioxide [Eq. (1)].[14] Although the cylinder-type reactor was suitable for product characterization, the reproducibility of the product yields was low. Therefore, detailed kinetics were examined with a flow-type reactor.

The hydrolysis of **1** in the flow-type reactor was carried out at 390 °C and water densities from 0.26 to 0.57 $g\,cm^{-3}$ for

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0.3–3.1 min, and the products and recovered **1** were analyzed by GLC.[15] The solution of **1** [$(2.5-3.8)\times10^{-3}$ M] was homogeneous even in ambient water and hence would remain homogeneous under the reaction conditions, because SCW dissolves organic compounds more readily than ambient water. The sum of **2**, ethylbenzene, and recovered **1** was 80–90% in all cases, and various uncharacterized low molecular weight products were also detected by GLC.

We also analyzed the first-order kinetics of the decarboxylation of **2** in SCW under similar conditions to evaluate the rate constant k_3. We obtained the pseudo-first-order rate constant k_1 for the hydrolysis of **1** according to Equations (2) and (3) under the assumption that the formation of the

$$\frac{d[\mathbf{1}]}{dt} = -(k_1+k_2)[\mathbf{1}] \tag{2}$$

$$\frac{d[\mathbf{2}]}{dt} = k_1[\mathbf{1}]-k_3[\mathbf{2}] \tag{3}$$

uncharacterized products takes place with a rate constant k_2 via an independent pathway. The results are summarized in Table 1. The most striking feature in Table 1 is that k_1 increases significantly with increasing pressure p and density ρ, while k_2 does not change (entries 1–5 and Figure 1). This observation partially proves the assumption that the uncharacterized products were formed via independent pathways.

Table 1. Hydrolysis of **1** in SCW at 390 °C [Eq. (1)].

Entry	p [MPa]	ρ [g cm^{-3}]	k_1+k_2[a]	k_1[a]	k_2[a]	k_3[a]	k_1'[b]
1	25.7	0.260	2.23	0.58	1.65	3.77	56.7
2	26.7	0.344	2.94	1.21	1.73	2.32	12.6
3	28.3	0.427	4.34	2.53	1.80	2.28	4.68
4	33.0	0.510	6.99	6.61	0.39	2.57	2.95
5	41.1	0.568	11.0	10.3	0.71	2.47	1.95
6[c]	28.3	0.427	3.57	1.78	1.79	2.28	n.d.[d]
7[e]	28.3	0.427	3.91	2.12	1.79	2.28	n.d.[d]

[a] $\times10^{-3}$ s^{-1}. [b] $\times10^{4}$ L mol^{-1} s^{-1}. [c] The reaction was carried out in the presence of 0.8 equiv of **2**. [d] Not determined. [e] The reaction was carried out in the presence of 1.6 equiv of **2**.

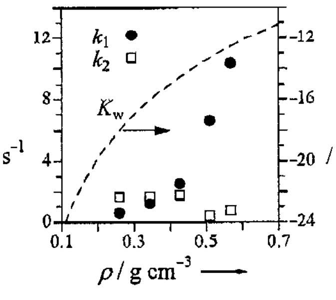

Figure 1. Rate constants k and the ionic product of water (K_w) as functions of the water density ρ. Correlation between the rate constant k_1 and the ionic product of water (K_w).

To clarify the origin of the observed density-dependent increase in k_1, we examined the correlation between k_1 and the ionic product of water (K_w), because K_w is also a function of the water density ρ, as is shown in Figure 1 (dotted line).[16] We found that k_1 has a linear correlation with the square root of K_w ($k_1 = k_1'K_w^{0.5}$; k_1' is the intrinsic rate constant), as shown in Figure 2.[17] As the square root of K_w is proportional to [H$^+$] and [OH$^-$], which catalyze ester hydrolysis under ambient conditions, the observed good correlation strongly suggests that the proton or the hydroxide ion dissociated from SCW promotes the hydrolysis.

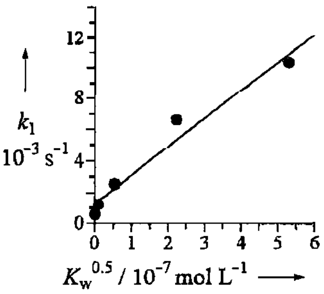

Figure 2. Correlation between the rate constant k_1 and the ion product of water k_w.

To determine the catalytic species, we examined the effects of protic acid on the rate by adding **2** and found that it had no effect on the rate (Table 1, entries 6 and 7). Under the conditions of entry 7, the initial proton concentration from dissociation of SCW was calculated to be 5.4×10^{-8} mol L^{-1}[16] and that from dissociation of **2** was 3.3×10^{-7} mol L^{-1}, by assuming that the dissociation constant of **2** is similar to that of 2-naphthoic acid in SCW.[10] Therefore, the results clearly indicate that protons have no effect on the hydrolysis under these conditions, and that hydroxide ions indeed catalyze the hydrolysis.[18]

Our conclusion seems to disagree with the previous report by Krammer and Vogel[9] on a rate enhancement by adding carboxylic acid. However, we believe that the discrepancy can be attributed to the concentration of the substrates; the initial concentration of the substrate and the added acid in our experiments is approximately 100–200 times lower than that of Krammer and Vogel.[19] Therefore, the effect of the protons generated from the carboxylic acid is negligible under our reaction conditions. Because the base-catalyzed hydrolysis proceeds about 1000 times faster than the acid-catalyzed hydrolysis under ambient conditions,[20] it is not surprising that the hydroxide ion catalyzed regime dominates over the proton-catalyzed one until the proton concentration from dissociation of the carboxylic acid greatly exceeds that of the hydroxide ions. Therefore, the hydroxide ion catalyzed reaction dominates over the proton-catalyzed reaction in the initial stage of the hydrolysis or under dilute conditions.

We also found that the rate of the hydrolysis was strongly affected by the dielectric constant ε. When we plotted the logarithmic intrinsic rate constant k_1' against the Kirkwood polarity parameter $(\varepsilon-1)/(2\varepsilon+1)$,[21] we observed an excellent linear correlation (Figure 3). The negative linear coefficient indicates that the rate of hydrolysis decreases with increasing dielectric constant. This result can be explained by considering the differences in charge localization between the reactants and the transition state (TS). Since the negative charge is more delocalized in the TS than

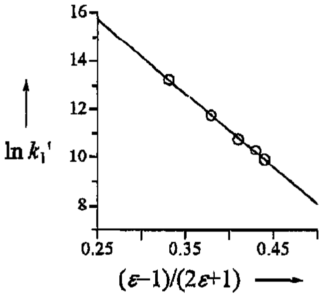

Figure 3. Correlation between the intrinsic rate constant k_1' and the Kirkwood polarity parameter.

in the reactants, the polar media must stabilize the reactants more efficiently than the TS. Consequently, the hydrolysis rate decreases with increasing water density.

In summary, we have demonstrated that the hydrolysis of esters takes place exclusively by ionic mechanisms, whereby hydroxide ions dissociated from SCW catalyze the reaction. This mechanism is dominant in the initial stage of the reaction, since the concentration of the generated carboxylic acid is low. As the concentration of carboxylic acid increases with the progress of the reaction, the mechanism would change to the proton-catalyzed reaction if the concentration of substrates were sufficiently high.[9] Our results clearly indicate that one must consider the involvement of hydroxide ions in other reactions in SCW, because dissociation of water produces the same amount of protons and hydroxide ions.

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[13] Cylindrical stainless steel (SUS316) or quartz tubes were used as reaction vessel. Similar results were obtained regardless of the vessel.

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[17] An alternative but less likely mechanism is the direct attack of a water molecule on the ester. Correlation of k_1 with k_1' and the concentration of water suggests that about four molecules of water participate in the transition state ($k_1 = k_1'[H_2O]^{3.7}$).

[18] Addition of sodium hydroxide (4.8×10^{-7} mol L^{-1}) enhanced the rate of hydrolysis by a factor of about 2.5. However, the lack of data on the dissociation constant of sodium hydroxide in SCW and the difficulties in obtaining an accurate value of k_3 prevented our making detailed kinetic analyses.

[19] Because of the low solubility of **1** in water, we could not directly compare the concentration effects.

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Modular Ligands for Asymmetric Synthesis: Enantioselective Catalytic Cu^{II}-Mediated Condensation Reaction of Ethyl Pyruvate with Danishefsky's Diene**

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The search for new catalysts for asymmetric synthesis is an area of significant importance in modern organic synthesis, and a number of spectacular advances have been reported in recent years.[1, 2] However, there is still a need for simple and readily available catalysts, particularly for C—C bond-forming processes.[3] A modular system that allows quick access to a great diversity of ligands from simple components is valuable. Peptide-based ligands have been developed for Ti-catalyzed additions of TMSCN to *meso* epoxides[4] and imines (Strecker amino acid synthesis),[5] and Zr-catalyzed addition of dialkylzincs to imines.[6] Recently, peptide-based phosphane ligands have been shown to promote efficient Cu-catalyzed conjugate addition.[7] Moreover, this class of ligands allows the regio- and enantioselective formation of quaternary carbon centers by using allylic reagents.[8] We report herein a simple and efficient approach that leads to the generation of a great diversity of asymmetric ligands from easily available components.[9]

The catalyst preparation is based on the condensation of 1,2-diamines[10] of type **1** with ketones or aldehydes **2** (Scheme 1), which affords imidazolidines **3** in solution in equilibrium with the open form **4**. The corresponding bis-imine **5** and the starting diamine **1** are often present with compounds **3** and **4** in the reaction mixture.[11] We anticipated that chelating metals such as Cu^{II} would shift this equilibrium toward the metallacyclic form **6** by forming a bidentate complex (Scheme 1).[12] Although no precedent for the use of

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